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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,850	DURDEN, DONALD L.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91-119* is/are pending in the application.

4a) Of the above claim(s) *115-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *91-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I with the species election of etoposides in the reply filed on 3/2/2007 is acknowledged. The traversal is on the ground(s) that groups I and II are related because the methods will result in a similar effect (i.e., modulation of PTEN activity which is associated with the initiation of angiogenesis). Groups I and II are methods for the treatment of cancer in a patient that involves PTEN signaling, and, therefore, do not comprise separate and distinct inventions. This is not found persuasive because group I uses the agonists and group II uses the antagonists. Therefore the active ingredients used for the claimed methods have the opposite effects, and must have different structures, which require divergent searches. This divergent search put a serious search burden on the examiner. Note the claimed invention is method of treating cancer. The requirement is still deemed proper and is therefore made FINAL.

Claims 91-119 are pending. Claims 115-119 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 91-114 are examined on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91-95, 97-101, 103-107, 109-111, and 113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 91, 110, and 112 as currently construed state that LY294002 is a "PTEN agonist", but claims 92, 113, and 114 as currently construed state that a PEN agonist effectively inhibits cancer cell metastasis is also LY294002. It is not clear whether there is any difference in scope of "PTEN agonist" or "PI3 kinase", or they are same entities with different names. The claims as currently construed says that each of the different functions of "PTEN agonist" different claims for example, claim 91 vs. claim 92 is the inherent characteristics of LY294002. The dependent claims are also rejected because they depend on the rejected base claims and the dependent claims are also indefinite as to the nature of the active ingredient being used for the claimed method.

For the purpose of this Office action, the Office would there is no difference in nature of the active ingredient for claims 91 and 92. However, this treatment does not relieve applicant the burden of responding to this rejection.

The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 91-95, 97-101, 103-107, 109-111, and 113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 91-95, 97-101, 103-107, 109-111, and 113 are drawn to a method using a genus of PTEN agonists, PI3 kinase inhibitors, AKT inhibitors.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a function of the genus. There is not even identification of any particular portion of a structure(s) that must be conserved in order to have the recited function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The specification at pages 44-45 discloses that the genus of PTEN agonist could be screened using the peptides listed at Table 1. The specification provides evidence for two art-known species, i.e. LY294002 and wortmannin for the claimed genus. Based on these two species, one cannot predict the types of PTEN agonists, PI3 kinase inhibitors, AKT inhibitors. Since the genus includes a large number of unpredictable species, possession of only two species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants adequately describes LY294002 and wortmannin.

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of PTEN agonists, PI3 kinase inhibitors, AKT inhibitors, given that the specification has only described LY294002 and wortmannin. Therefore, only LY294002 and wortmannin, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 91-95, 97-101, 103-107, 109-111, and 113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling** for method using LY294002 and Wortmannin, and TNF alpha for effectively inhibiting aberrant tumor-associated angiogenesis, does not reasonably provide enablement for any other

PTEN agonist, PI3 kinase inhibitor, AKT inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 91-95, 97-101, 103-107, 109-111, and 113 are drawn to a method of effectively inhibiting aberrant tumor-associated angiogenesis comprising administering a genus of active ingredients named "PTEN agonist", "inhibitor of PI3 kinase", "inhibitor of AKT". The specification fails to provide enablement for the claims drawn to method of using LY294002 and Wortmannin. However, the specification does not provide how to make other PTEN agonist, PI3 or AKT inhibitor. The teaching of the specification is limited to method of treating cancer by inhibiting aberrant angiogenesis (see Fig. 15, page 74 Example IV).

It is well known that the art of anticancer drug discovery for cancer therapy by any mechanism including inhibiting aberrant angiogenesis is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to

make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are

unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). In addition, the specification does not teach how to deliver an ATK inhibitor to the proper site of action, which appears to be cytosol according to 2nd para, col 1 at page 1751 of Jiang et al (02-15-2002, PNAS vol. 97, pages 1749-1753). The specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the formulation. The specification provides insufficient guidance how to make an ATK inhibitor, PI3 kinase, or PTEN agonist other than the art-known LY294002 and wortmannin, and other issues raised above, and unpredictability in art as regard to cancer treatment, broad breath of the claims, it is concluded that undue experimentation would be required to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 91, 92, 95, 96, 98, 104, and 110-114 are rejected under 35 U.S.C. 102(a) as being anticipated by Hu et al (March 2000, Clinical Cancer Research, vol. 6, pages 880-886) as evidenced by Jiang et al (02-15-2002, PNAS vol. 97, pages 1749-1753).

Claims 91, 92, 95, 96, 98, 104, and 110-114 are drawn to method of treating cancer comprising administering an effective amount of LY294002 (as a PTEN agonist, note the claim construction of claims 91, 110, and 112) to a cancer patient, wherein the PTEN agonist effectively inhibits aberrant tumor-associated angiogenesis.

Hu et al., teach method of treating cancer comprising administering LY294002 to tumor-bearing mice, which is same as "a patient in need thereof". Although Hu et al., do not teach the mechanism of action of LY294002 to be inhibiting aberrant tumor-associated angiogenesis, the claimed method is anticipated by Hu et al., because the method will inherently lead to inhibit aberrant angiogenesis on the tumor cells. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Note Jiang et al., for mechanism of action of PI3 kinase inhibitor. Hu et al., do not teach LY294002 being "PTEN" agonist. However, the preferred embodiment "LY294002" in claim 112 is PTEN agonist since the dependent claim further limits "PTEN agonist" of the base claim 91. The limitation "further comprising" in claim 95 and applicable claims are interpreted as adding one than one dose of the same active ingredient. As for claim 110 and 111, where the

function of the active agent (ATK kinase or PI3 kinase inhibiting PTEN agonist) in the claimed method is to induce apoptosis (claim 110) and p53 medicated-apoptosis (claim 111), the instant specification at Example IV and Fig, 14, discloses LY294002 induces p53 medicated-apoptosis. As for claim 92, PTEN agonist effectively inhibits cancer cell metastasis, claim 114 says that LY294002 has the function recited in claim 92. As for the limitations of "enhancing claims 98 and 1

Thus, Hu et al., anticipate claims 91, 92, 95, 96, 98, 104, and 110-114.

Claims 91, 95, and 110 are rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al Anticancer Res. 1995 Jul-Aug;15(4):1135-9, as evidenced by Oikawa et al (1996, European Journal of Pharmacology, vol. 318, pages 93-96) discloses Wortmannin inhibits angiogenesis

Schultz et al., teach (at Table III-V) method of cancer treatment comprising administration of an effective amount of Wortmannin to a patient in need thereof (in vivo human tumor xenograft models). Although Schultz et al., do not teach that Wortmannin effectively inhibit aberrant tumor-associated angiogenesis, the claimed method is anticipated by Schultz et al., because the method will inherently lead to inhibit aberrant angiogenesis on the tumor cells. Since instant claim 110 reasonably communicates that a compound that inhibits "PI3 kinase activity" is PTEN agonist. Wortmannin, which is a PI3 kinase activity meet the limitation of "PTEN agonist". The instant claim 95 says that "an inhibitor of PI3 kinase" is a P See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Note Oikawa et al., for mechanism of action. Note Oikawa et al., teach Wortmannin is potent inhibitor of angiogenesis (note the title).

Claims 91-94, and 98-100 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6783760 B1 (the effective filing date of Jul. 12, 1999) as evidenced by Stambolic et al., 1998, Cell, vol. 95, pages 29-39.

Claims 91 method of cancer treatment comprising administering PTEN agonist, wherein said agonist effectively inhibits aberrant tumor-associated angiogenesis (claim 91), effectively inhibits caner cell metastasis (claim 92), the method further comprising one additional chemotherapeutic agent in claims 98-100 (etoposides as the elected species) in claims 93, 94, wherein said at least one agonist is effective to enhance the chemosensitivity (claim 98) cells in the cancer,

US 6783760 B1 teach method of treating cancer comprising administering TNF-α (note claims 33 and 34), which inhibit aberrant tumor-associated angiogenesis, and additional chemotherapeutic agent of etoposides (claim 39). Although the patent does not teach TNF-α is PTEN agonist, Stambolic et al., at Figure 4 at page 32 and abstract teach that TNF-α is PTEN agonist. As for the instant claim 92 (i.e. inhibiting metastasis), the patent at Paragraph 129, teach "the anti-cancer agent is an anti-angiogenic agent designed to prevent micrometastasis of any remaining tumor cells.

As for at least one agonist being effective to enhance the chemosensitivity in the instant claim 91, the patent at Paragraph 412-4 discloses;

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In certain embodiments, the therapeutic agent-targeting agent constructs of the present invention may be administered in combination with a chemotherapeutic agent. Chemotherapeutic drugs can kill proliferating tumor cells, enhancing the necrotic areas created by the overall treatment. The drugs can thus enhance the thrombotic action of the therapeutic agent-targeting agent constructs.

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By inducing the formation of thrombi in tumor vessels, the therapeutic agent-targeting agent constructs can enhance the action of the chemotherapeutics by retaining or trapping the drugs

within the tumor. The chemotherapeutics are thus retained within the tumor, while the rest of the drug is cleared from the body. Tumor cells are thus exposed to a higher concentration of drug for a longer period of time. This entrapment of drug within the tumor makes it possible to reduce the dose of drug, making the treatment safer as well as more effective.

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Irrespective of the underlying mechanism(s), a variety of chemotherapeutic agents may be used in the combined treatment methods disclosed herein. Chemotherapeutic agents contemplated as exemplary include, e.g., tamoxifen, taxol, vincristine, vinblastine, etoposide (VP-16), adriamycin, 5-fluorouracil (5FU), camptothecin, actinomycin-D, mitomycin C, cisplatin (CDDP), combretastatin(s) and derivatives and prodrugs thereof.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 91-92, 95-96, 101-102, 104, and 110-114 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,777,439. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims 1-3 of U.S. Patent No. 6,777,439 are species of the genus claimed in the instant claims 91-92, 95-96, 101-102,

104, and 110-114. Claims 1-3 of the patent have additional step of assessing angiogenesis. However, the instant claims construed with the open transitional phrases "comprising" do not exclude the assessing step.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MISOOK YU, Ph.D.
Primary Examiner
Art Unit 1642